Amendments to the Specification

Please delete the paragraph on page 12, lines 12-14 and replace it with the following paragraph:

Figure 4A is a Coomassie blue stained gel of 6XHis **(SEQ ID NO: 39)** -tagged recombinant yeast (r-y Sir2p) and murine (r-m Sir2α) Sir2 proteins purified with Ni-NTA agarose under native conditions. Arrowheads indicate each full-length protein.

Please delete the paragraphs on page 16, lines 1-7 and replace it with the following paragraphs:

Figure 14a is the amino acid sequence of the core domains of ySir2p (**ySir2;** SEQ ID NO: 11), mSir2α (SEQ ID NO: 12) and CobB (SEQ ID NO: 13) aligned and six highly conserved residues, indicated by arrowheads, were mutated to alanine.

Figure 14b shows the 6XHis **(SEQ ID NO: 39)** tagged versions of wild type ySir2p (wt) and the six mutant Sir2p (Thr-261, Gly-270, Iso-271, Arg-275, Asn-345, Asp-347) and a vector control (vector) expressed in *E. coli*, purified over a Nickel-NTA column and analyzed on a 7% polyacrylamide SDS gel to assess expression levels.

Please delete the paragraph on page 70, lines 11-18 and replace it with the following paragraph:

The yeast *SIR2* gene or the mSIR2a full-length cDNA was cloned into pET28a vector (Novagen). BL21(DE3) and BL21(DE3)pLysS with an extra copy of arginine tRNA gene was transformed with the ySIR2 and mSIR2α plasmids, respectively. Each transformed bacterial clone was induced in 1mM IPTG at 37^0C for 1hr. The induced 6XHis **(SEQ ID NO: 39)** -tagged proteins were purified with Ni-NTA agarose under native condition (see Figure 4A). The N-terminal fragment of mSir2 α was prepared in the same way. The control elute was prepared from a bacterial clone carrying pET28a vector only. The recombinant proteins were aliquoted and kept at -70^0C.

Please delete the paragraph on page 72, lines 20-26 and replace it with the following paragraph:

The yeast *SIR2* gene or the *mSIR2α* full-length cDNA was cloned into pET28a vector (Novagen). BL21(DE3) and BL21(DE3)pLysS with an extra copy of arginine tRNA gene was transformed with the *ySIR2* and *mSIR2α* plasmids, respectively. Each transformed bacterial clone was induced in 1mM IPTG at 37^{0}C for 1hr. The induced 6XHis **(SEQ ID NO: 39)** -tagged proteins were purified with Ni-NTA agarose under native conditions. The control elute was prepared from a bacterial clone carrying pET28a vector only. The recombinant proteins were aliquoted and kept at -70^{0}C.

Please delete the paragraph on page 88, lines 6-17 and replace it with the following paragraph:

A set of mutations in highly conserved residues of the core domain of *SIR2* were constructed by site-directed mutagenesis (Figure 17a) and cloned into vectors, along with the wild type, to allow expression of the recombinant proteins in *E. coli* or expression of single-copy genes from the native *SIR2* promoter in *S. cerevisiae*. These 6Xhis **(SEQ ID NO: 39)** tagged proteins were purified from E. coli by a Ni-NTA column (Figure 17b) and analyzed for the NAD-dependent histone H3 deacetylase activity in an assay with a di-acetylated H3 peptide (residues 1-20 acetylated on Lys9 and Lys14) and 1mM NAD. HPLC separation of the reaction products yields five peaks of which 1, 2, a portion of 3 and 4 are deacetylated species of peptide (Figure 15). In this deacetylase assay, mutants 345 and 347 were inactive, mutant 261 showed 17% of wild type activity, mutants 270 and 271 showed 80% and 36% wild type activity, respectively, and mutant 275 showed 67% wild type activity.